SBRT for Prostate Cancer

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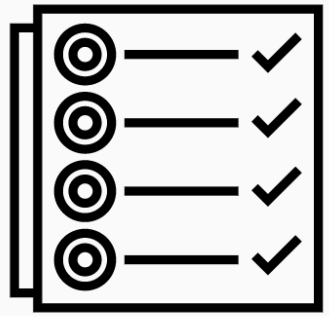
Objectives



To review key aspects of prostate cancer SBRT for radiation oncology trainees through a case vignette

1. Recognize the indications for prostate SBRT
2. Learn about the differences between ultrahypofractionation and more protracted fractionation schemes
3. Review the major clinical trials, retrospective studies and practice guidelines
4. Understand practical treatment planning considerations

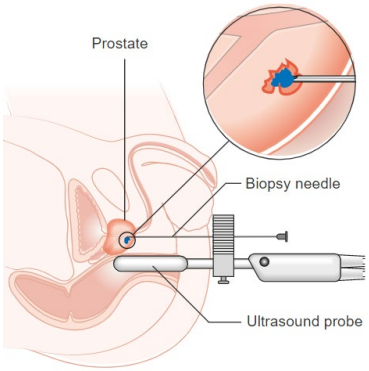
Case

- 50-year-old male presented to his primary care physician with dysuria and was referred to Urology.
- He was found to have an elevated PSA:
- ECOG: 0; KPS: 100
- IPSS 8; SHIM: 21

PSA	2 years ago	1 year ago	Most recent
	3.02	3.46	4.02

- PMHx: h/o DVT, BPH, microhematuria with a negative CT abdomen/pelvis, dysuria, intermittent erectile dysfunction, arthritis, GERD
- SurgHx: Hernia repair, cholecystectomy
- SocHx: No smoking, alcohol or illicit drug use
- Meds: Eliquis, Flomax
- FMHx: Father, paternal uncles, maternal grandfather and maternal uncles had prostate cancer
- Physical Exam: Appears to be of his stated age in no distress. Enlarged prostate with no palpable nodules or evidence of extraprostatic extension or SV involvement. No bone tenderness.

Case



- Systematic TRUS biopsy: Gleason 3+3=6 in 3 out of 12 cores in the right mid lateral and right lateral apex. Up to 60% of a core was involved. Grade group 1.
- Prostate volume: 45 cc.
- AJCC 8th edition T1cN0M0, Stage I
- NCCN low-risk prostate. Calculated life expectancy using Social Security Actuarial Life Table (https://www.ssa.gov/oact/STATS/table4c6.html) is 30 years.

Brief Overview of Localized Prostate Cancer Treatment Options

- Watchful waiting
- Active surveillance
- Radical prostatectomy
- Definitive radiotherapy +/- ADT
  - Conventionally-fractionated
  - Hypofractionated
  - Ultrahypofractionated
  - Brachytherapy
  - EBRT + brachytherapy

Rationale for using SBRT in Prostate Cancer

- Low alpha/beta ratio of 1.5-1.8 (CHHiP trial and Perez and Brady)
- If the alpha/beta for dose-limiting normal tissue is less than that of the tumor, larger fraction sizes preferentially kill the tumor compared to normal tissue
- Increased patient convenience
- Increased access for underserved patient populations (long commute etc)
- More cost-effective than other EBRT fractionation schedules

Dearnaley *et al* Lancet Oncol 2016, Halperin *et al* Principle and Practice of Radiation Oncology, Ju *et al* JCO 2014, Sher *et al* Am J of Clin Oncol 2014

Indications for SBRT in Prostate Cancer

- NCCN 2020: very low, low, favorable intermediate, unfavorable intermediate, high, very high-risk prostate cancer and low volume M1 disease
- ASTRO, ASCO and AUA 2018: low and intermediate-risk disease
- 2020 COVID19 pandemic recommendation: 5- to 7-fraction SBRT is preferred for localized prostate cancer that requires treatment

Schaeffer *et al* NCCN 2020, Morgan *et al* J Urol 2018, Zaorsky *et al* Advances in Radiation Oncology 2020

HYPO-RT-PC

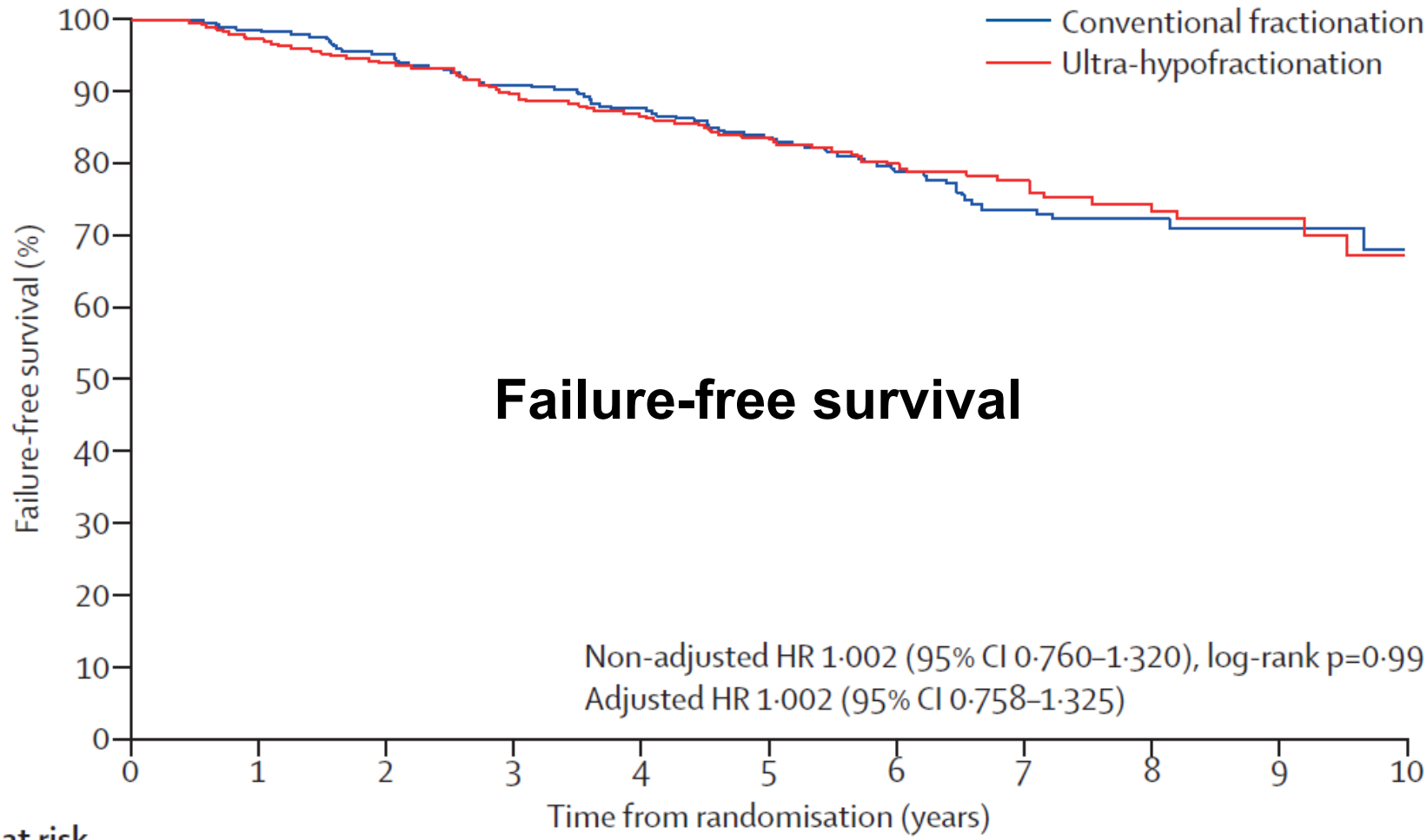
- Phase 3 non-inferiority randomized trial in 12 centers in Sweden and Denmark
- Men up to 75 years of age with intermediate-to-high-risk prostate cancer
- 1200 patients, 89% were intermediate risk, median follow-up: 5 years
- SBRT (42.7 Gy in 7 fractions) vs conventional fractionation (78 Gy in 39 fractions) with **no ADT**

Widmark *et al* Lancet 2019

HYPO-RT-PC

- No difference in oncologic outcomes (SBRT was non-inferior to 78 Gy in 39 fractions)
  - 5-year failure-free survival was 84% in both groups at 5 years (HR 1.002, 95% CI 0.758-1.325; p = 0.99)
- No difference in physician-reported GI, GU or sexual toxicity except for increased urinary toxicity at one year for SBRT (6% vs 2%)
- Patient-reported outcomes with Prostate Cancer Symptom Scale (PCSS): greater acute urinary and bowel symptoms with SBRT but no difference in chronic symptoms except for urinary toxicity at one year (also worse with SBRT)

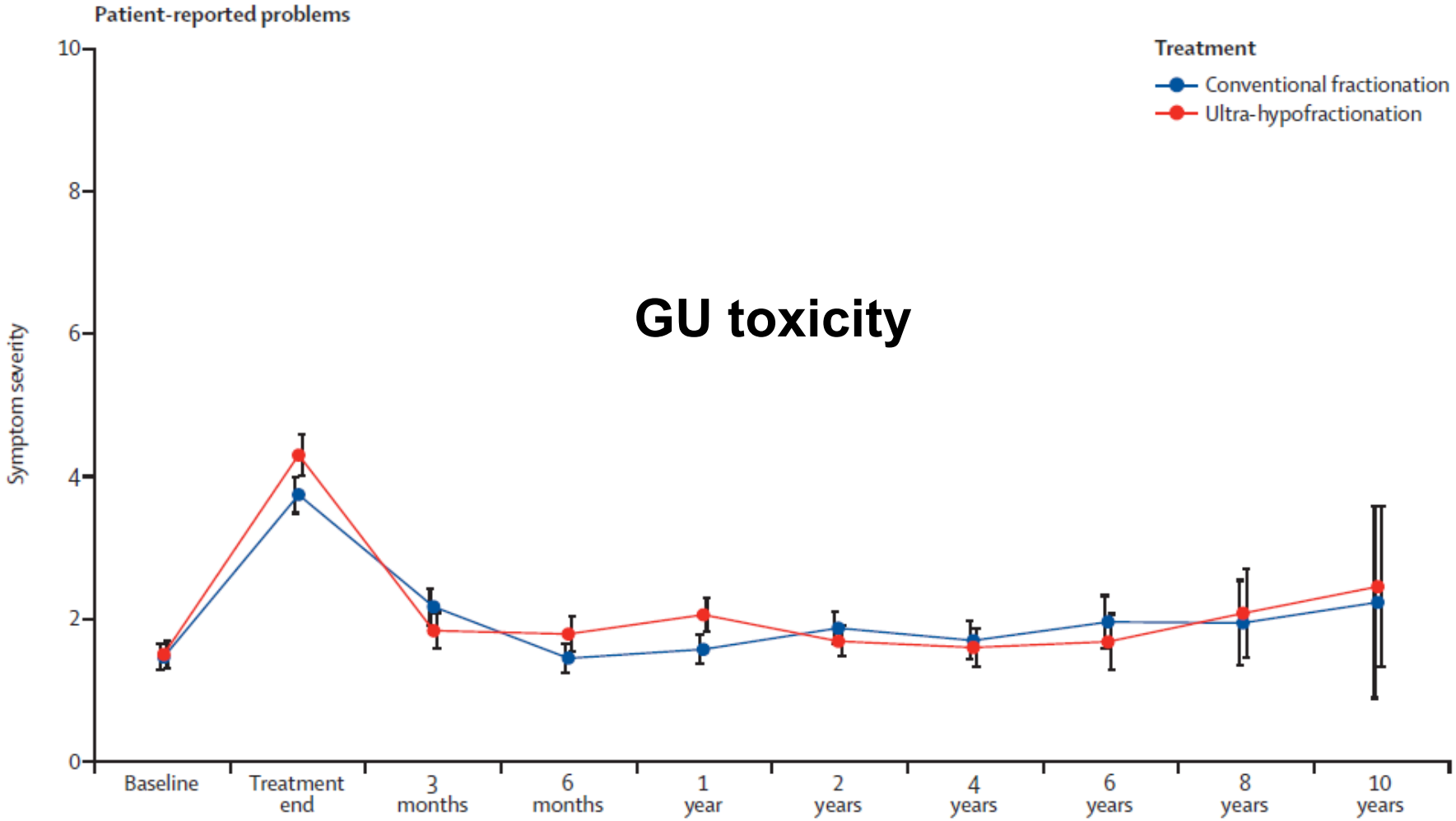
Widmark *et al* Lancet 2019



Failure-free survival

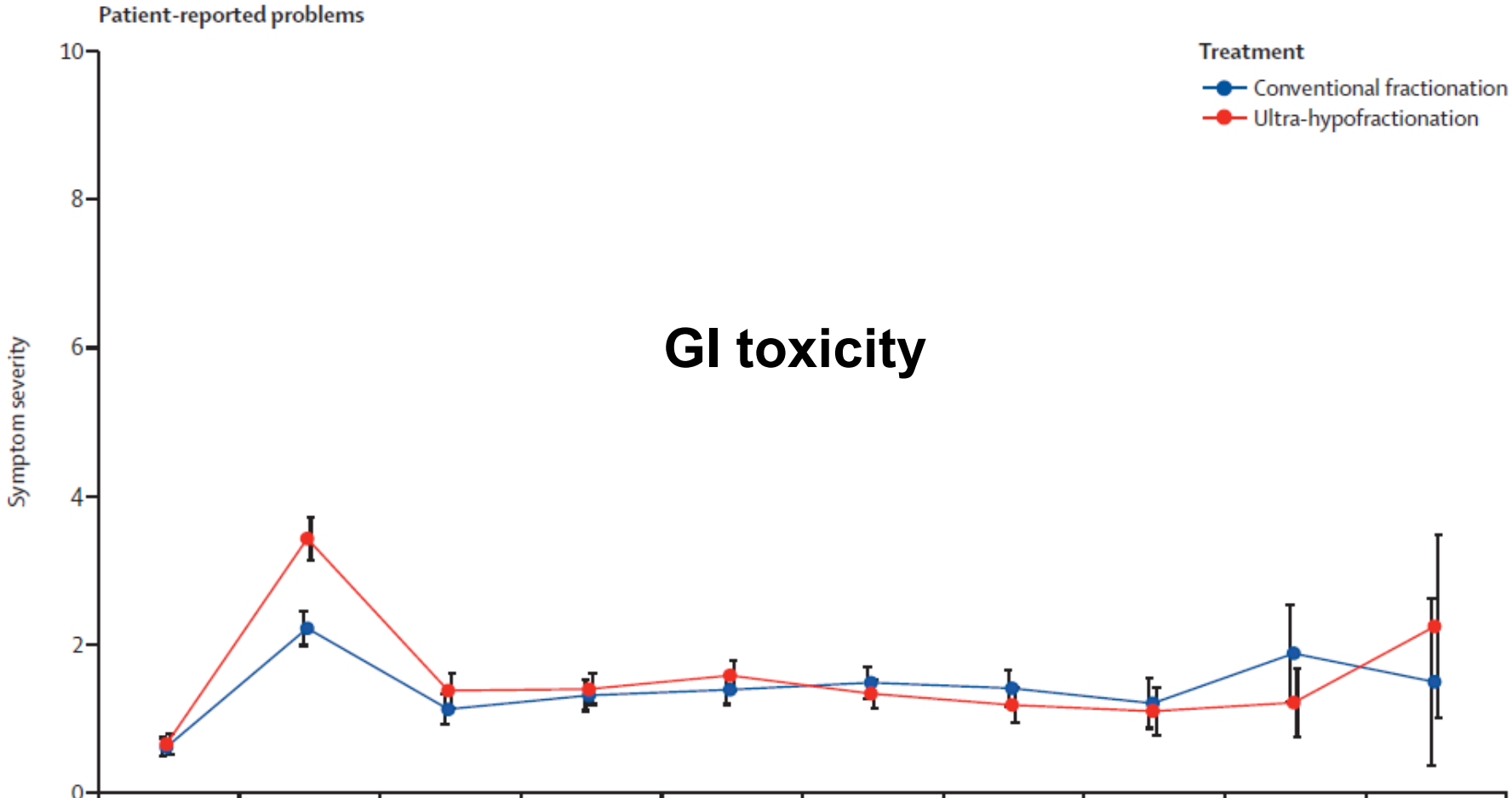
Number at risk (number censored)											
Conventional fractionation	591 (0)	580 (4)	540 (24)	433 (108)	332 (196)	242 (273)	171 (332)	108 (386)	67 (425)	37 (454)	23 (467)
Ultra-hypofractionation	589 (0)	569 (4)	527 (27)	408 (125)	325 (196)	242 (269)	160 (342)	113 (385)	71 (423)	38 (454)	20 (470)

GU toxicity



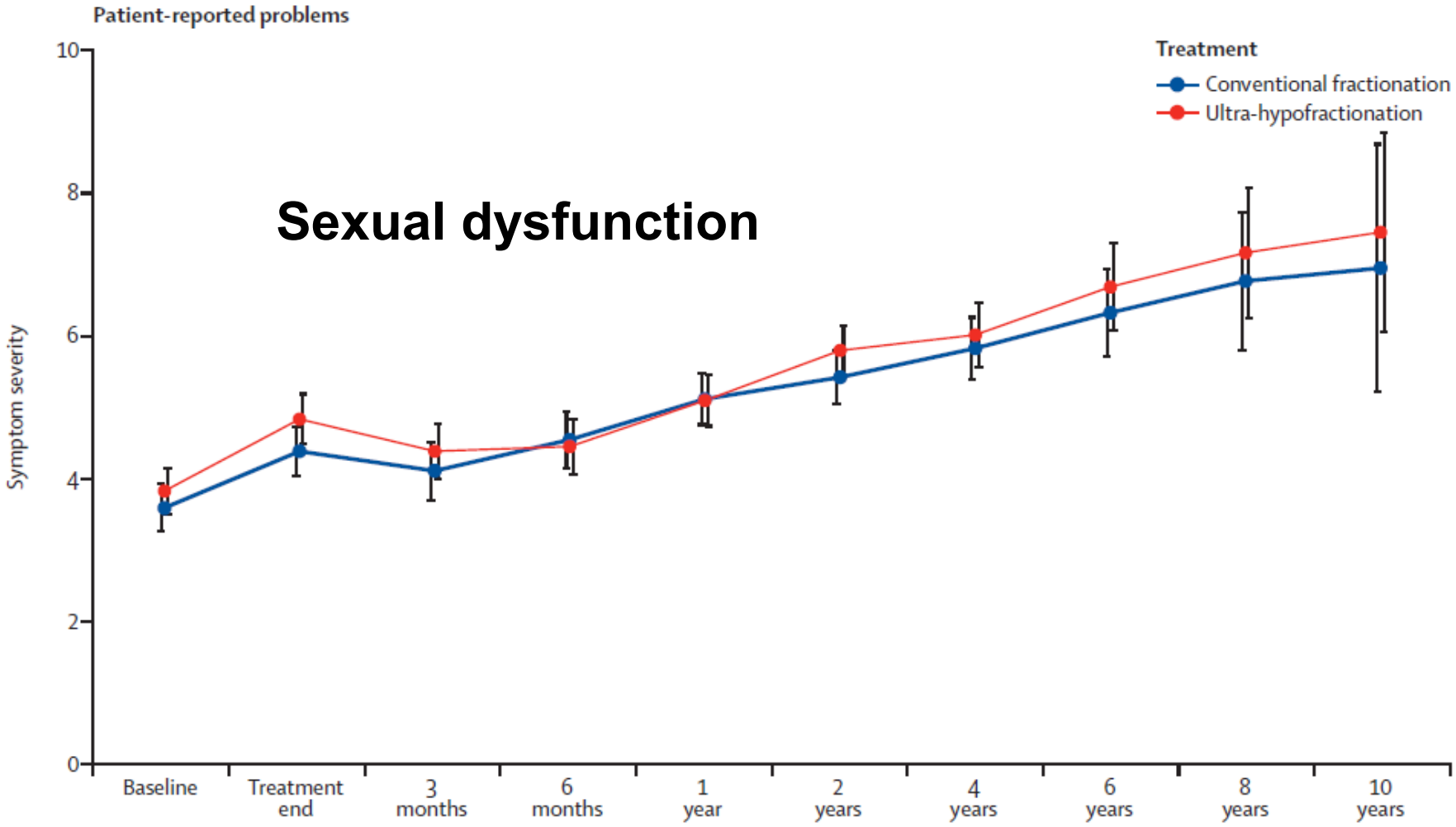
Number assessed	Baseline	Treatment end	3 months	6 months	1 year	2 years	4 years	6 years	8 years	10 years
Conventional fractionation	468	464	336	347	427	404	272	156	59	21
Ultra-hypofractionation	478	439	330	358	425	425	275	143	72	24
p value	0·78	0·0066	0·018	0·16	0·0036	0·18	0·49	0·19	0·98	0·57

GI toxicity



	Baseline	Treatment end	3 months	6 months	1 year	2 years	4 years	6 years	8 years	10 years
Number assessed										
Conventional fractionation	469	463	329	346	423	404	273	152	61	22
Ultra-hypofractionation	485	440	335	359	426	427	277	145	73	24
p value	0·93	<0·0001	0·26	0·42	0·059	0·32	0·20	0·75	0·035	0·30

Sexual dysfunction

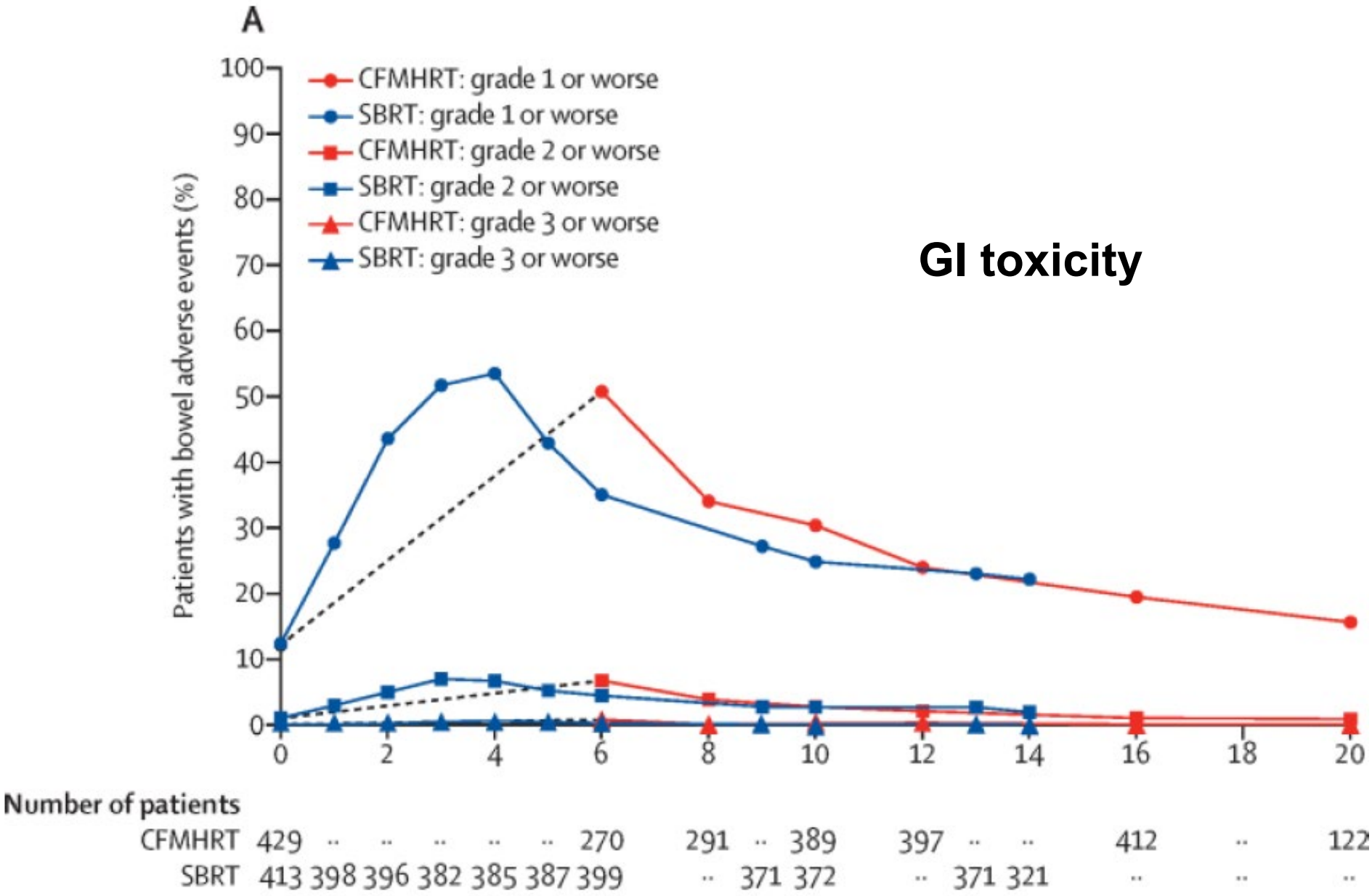


Number assessed										
Conventional fractionation	453	443	318	331	412	396	266	153	61	21
Ultra-hypofractionation	470	414	319	346	410	405	260	135	66	22
p value	0·31	0·066	0·28	0·62	0·74	0·18	0·57	0·41	0·47	0·90

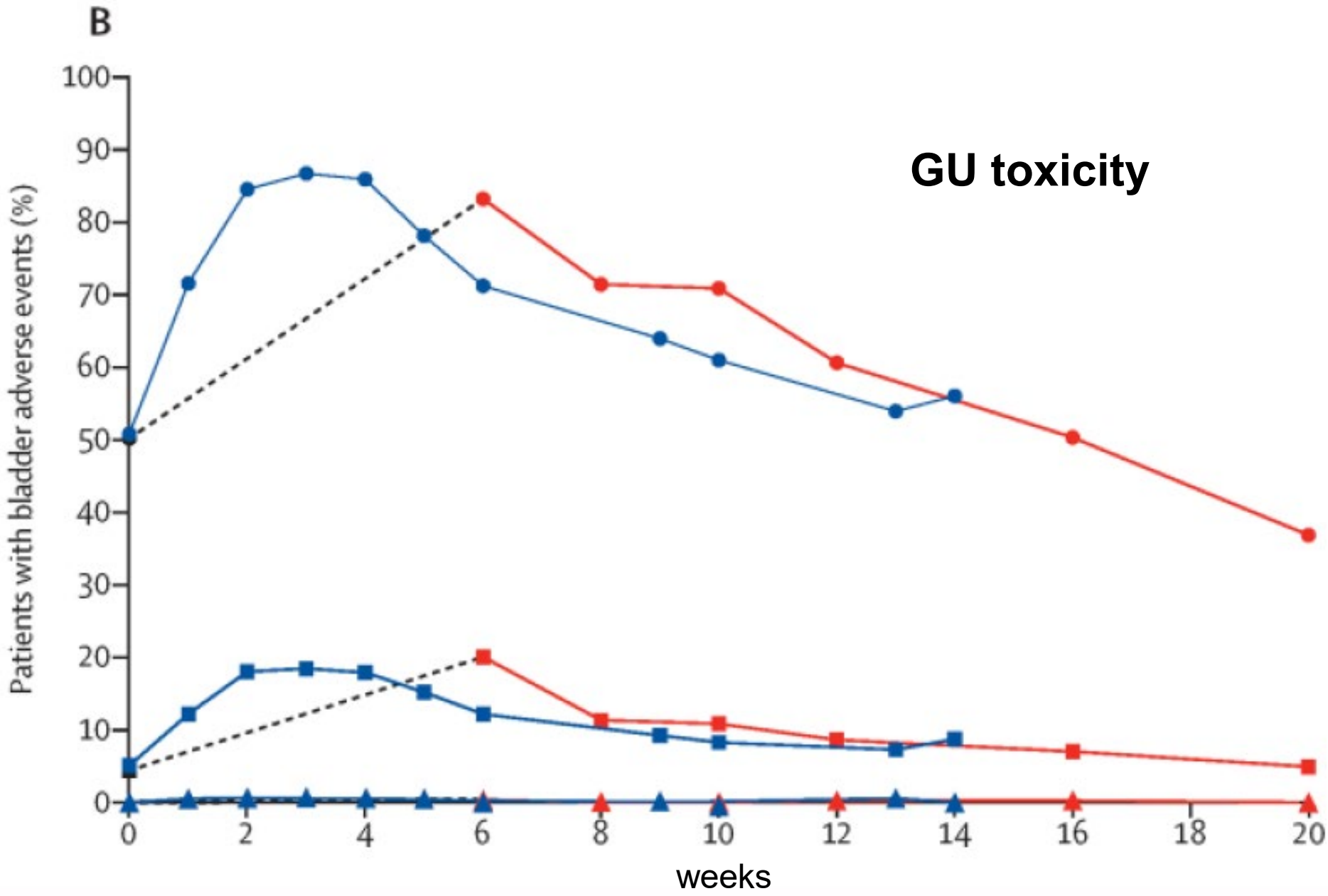
PACE-B

- Phase 3 non-inferiority randomized trial in 37 centers in UK, Ireland and Canada
- Low to favorable intermediate risk prostate cancer
- 874 patients, 85% Gleason Score 3+4=7, median follow-up: 12 weeks
- SBRT (36.25 Gy in 5 fractions with a concomitant boost to 40 Gy) vs conventionally fractionated or moderately hypofractionated EBRT (78 Gy in 39 fractions or 62 Gy in 20 fractions) with **no ADT**
- Unlike HYPO-RT-PC, there was no difference in toxicity with SBRT including patient-reported outcomes
- GI and GU toxicity timing differed: occurred earlier during treatment and resolved faster with SBRT
- **Oncologic outcomes are not yet available**

Brand *et al* Lancet Oncol 2019

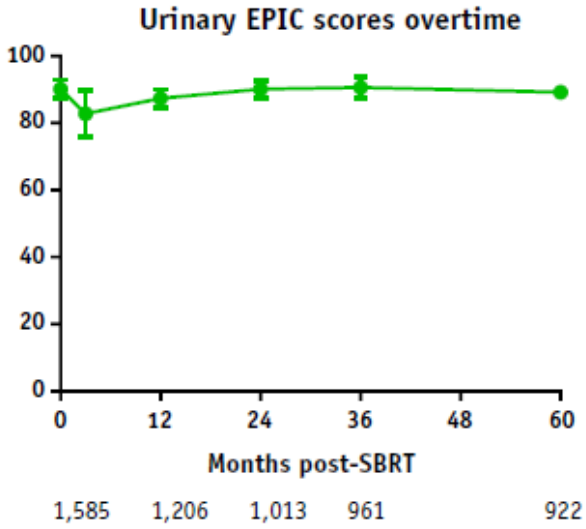

A
CFMHRT: grade 1 or worse
SBRT: grade 1 or worse
CFMHRT: grade 2 or worse
SBRT: grade 2 or worse
CFMHRT: grade 3 or worse
SBRT: grade 3 or worse
Patients with bowel adverse events (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
Number of patients
CFMHRT 429 .. .. 270 291 .. 389 397 .. .. 412 .. 122
SBRT 413 398 396 382 385 387 399 .. 371 372 .. 371 321 .. .. ..
weeks

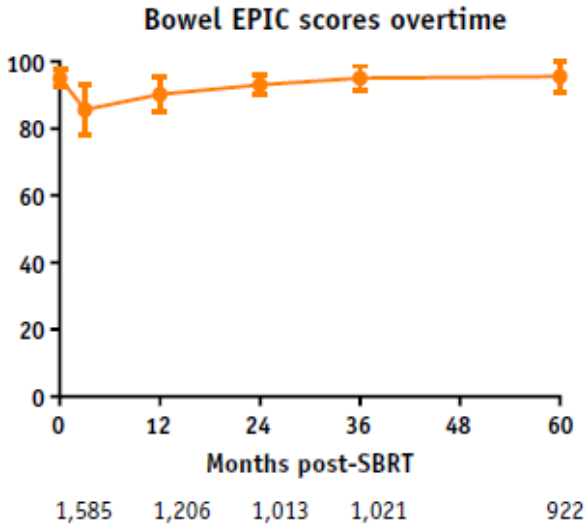
GI toxicity

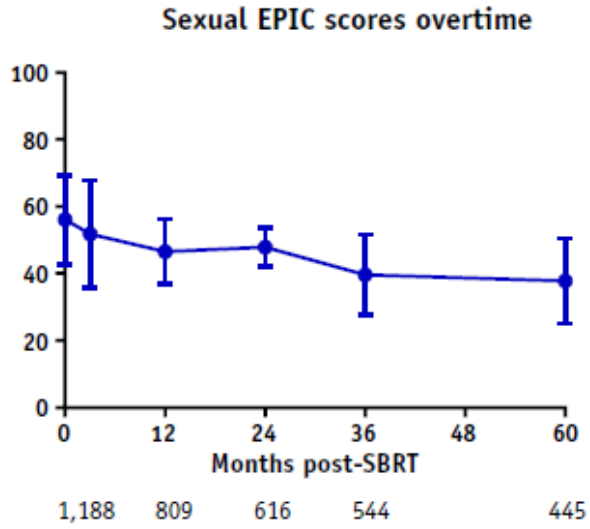

B
GU toxicity
Patients with bladder adverse events (%)
100
90
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
16
18
20
weeks

Retrospective Data

- Jackson et al meta-analysis
  - 38 prospective trials with 6116 patients including low, intermediate and high-risk patients
  - 7-year biochemical relapse free survival (bRFS) was 93.7%, late >=3 GU and GI toxicity rates were 2% and 1.1%

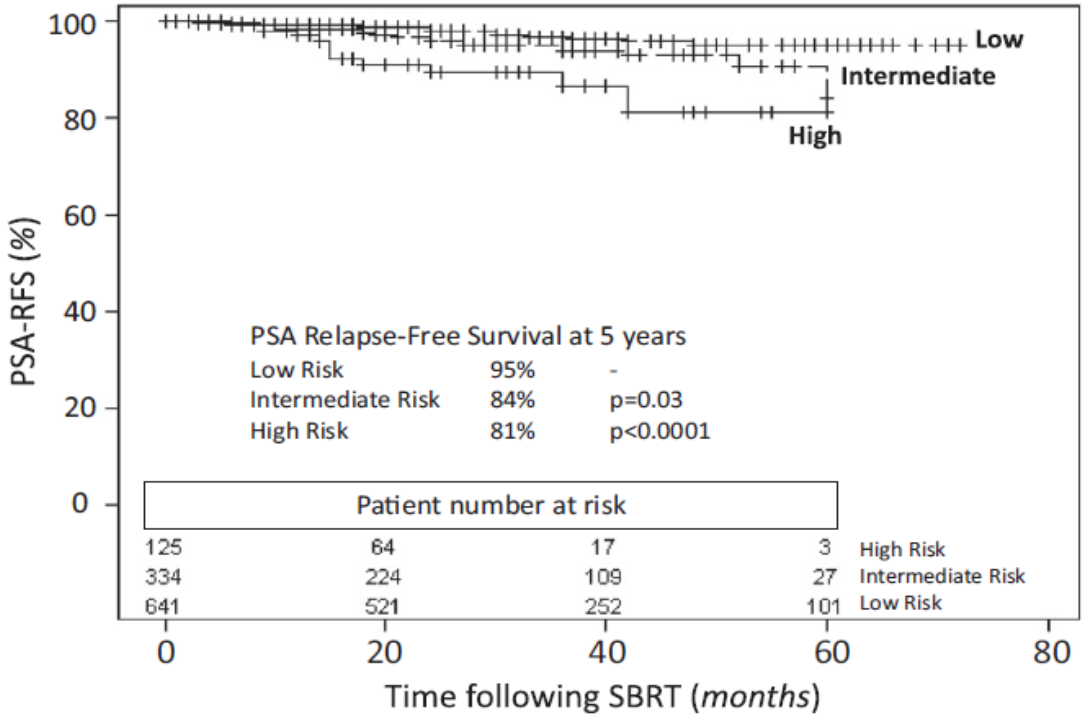






Jackson *et al* IJROBP 2019

- King et al
  - pooled analysis of prospective trials from 8 institutions with a total of 1100 patients
  - 5-year bRFS was 93%
  - No difference in outcome with ADT use
  - PSA bounce > 0.2 ng/ml was noted in 16% of patients



King *et al* Radiotherapy and Oncology 2013

- Kishan et al
  - pooled analysis of prospective trials from 10 institutions with a total of 2142 patients
  - 7-year bRFS was 95.5% for low-risk, 91.4% for favorable intermediate-risk and 85.1% for unfavorable intermediate-risk disease

Toxic Event	Crude Incidence, No. (%)[b]	Cumulative Incidence Estimate (95% CI)		
		5 y	7 y	10 y
Grade 2				
Acute GU	153 (9.0)	NA	NA	NA
Acute GI	56 (3.3)	NA	NA	NA
Late GU	163 (9.6)	11.2 (9.7-12.8)	12.3 (10.8-14.0)	13.4 (11.6-15.4)
Late GI	67 (3.9)	4.5 (3.6-5.6)	4.5 (3.6-5.6)	4.5 (3.6-5.6)
Grade ≥3				
Acute GU	13 (0.6)	NA	NA	NA
Acute GI	2 (0.09)	NA	NA	NA
Late GU	46 (2.1)	1.8 (1.3-2.5)	2.4 (1.8-3.2)	3.2 (2.2-4.6)
Late GI	7 (0.3)	0.4 (0.2-0.8)	0.4 (0.2-0.8)	0.4 (0.2-0.8)

Kishan *et al* JAMA Network Open 2019

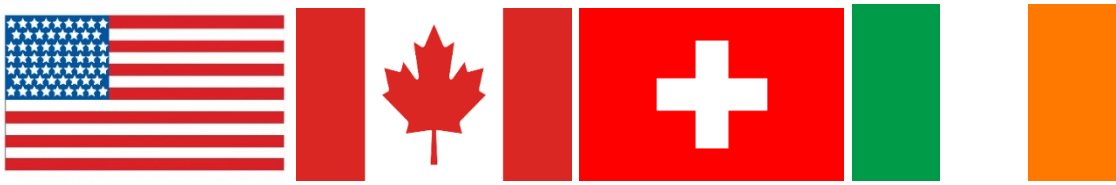
Table 1. Individual Prospective Study Characteristics

Source	Years Treated	No. of Patients	Follow-up, Median (Range), y	Dose/Fraction (% of Patients Who Received Dose/Fraction)	Prescription Specification, %	Risk Group, %
Masen et al,[16] 2007	2000-2004	40	5.9 (0.7-15.0)	6.7 Gy ×5	90 Of prescribed dose to cover 100 of GTV	100 Low
King et al,[17] 2012	2003-2009	67	9.5 (3.3-13.3)	7.25 Gy ×5	100 Of prescribed dose to cover 95 of PTV	73 Low, 15 Fav Int, and 2 Unfav Int
Katz and Kang,[18] 2014	2006-2010	477	7.9 (0.5-9.9)	7 Gy ×5 (32) and 7.25 Gy ×5 (68)	100 Of prescribed dose to cover 95 of PTV	68 Low, 22 Fav Int, and 9.8 Unfav Int
Mantz,[19] 2014	2007-2012	415	7.7 (5.0-10.4)	8 Gy ×5	100 Of prescribed dose to cover 98 of PTV	68.2 Low, 27 Fav Int, and 5 Unfav Int
Meier et al,[20] 2018	2008-2011	141	5.0 (0.1-8.2)	7.25 Gy ×5	100 Of prescribed dose to cover 95 of PTV	35 Low, 33 Fav Int, and 31 Unfav Int
Fuller et al,[21] 2018	2007-2012	206	5.0 (0.1-9.6)	9.5 Gy ×4	100 Of prescribed dose to cover 95 of PTV	43 Low, 35 Fav Int, and 21 Unfav Int
Alayed et al,[22] 2018	2006-2008	84	9.6 (1.0-10.8)	7 Gy ×5	95 Of prescribed dose to cover 99 of PTV	100 Low
Alayed et al,[22] 2018	2010	30	6.8 (5.7-7.2)	8 Gy ×5	95 Of prescribed dose to cover 99 of PTV	60 Low, 30 Fav Int, and 10 Unfav Int
McBride et al,[23] 2012	2006-2011	135	6.3 (0.1-10.3)	7.25 Gy ×5	100 Of prescribed dose to cover 95 of PTV	35 Low, 31 Fav Int, and 34 Unfav Int
UCLA[24]	2010-2012	95	6.0 (0.3-8.1)	8 Gy ×5	100 Of prescribed dose to cover 95 of PTV	91 Low, 5 Fav Int, and 4 Unfav Int
Fuller et al,[25] 2014	2006-2012	51	6.0 (1.7-10.1)	9.5 Gy ×4	100 Of prescribed dose to cover 95 of PTV	1 Low, 71 Fav Int, and 28 Unfav Int
Kataria et al,[26] 2017	2007-2012	402	4.3 (1.8-9.1)	7 Gy ×5 (33) and 7.25 Gy ×5 (67)	100 Of prescribed dose to cover 95 of PTV	36 Low, 48 Fav Int, and 16 Unfav Int
Total	2000-2012	2142	6.9 (0.1-15.0)	NA	NA	65 Low, 25 Fav Int, and 9.9 Unfav Int

Kishan *et al* JAMA Network Open 2019

Ongoing Trials

- Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in Treating Patients With Stage IIA-B Prostate Cancer NRG GU005
  - IMRT vs SBRT



- Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer (HEAT)
  - 70.2 Gy in 26 fractions vs 36.25 Gy in 5 fractions
  - Low and intermediate risk disease included

Back to the Case

- Treatment options for low-risk prostate adenocarcinoma including active surveillance (preferred), radical prostatectomy and radiotherapy were discussed
- Germline testing was considered due to positive family history, but the patient declined it
- Patient decided on definitive radiotherapy due to concern over cancer progression given his age and family history
- SBRT was chosen due to convenience

Technical Considerations

- Prostate size: prostate volume has to be < 60 cc to be included on GU005
- IPSS: has to be < 15 on GU005
- Comorbidities and anticoagulation: consider prior to fiducial marker/SpaceOAR placement
- Anesthesia considerations
- Multi-parametric MRI prostate (mpMRI) and DRE: rule out locally-advanced disease and extraprostatic extension is a counterindication to SpaceOAR placement
- Risk of pelvic lymph node involvement: estimate to determine if lymph node irradiation may be indicated

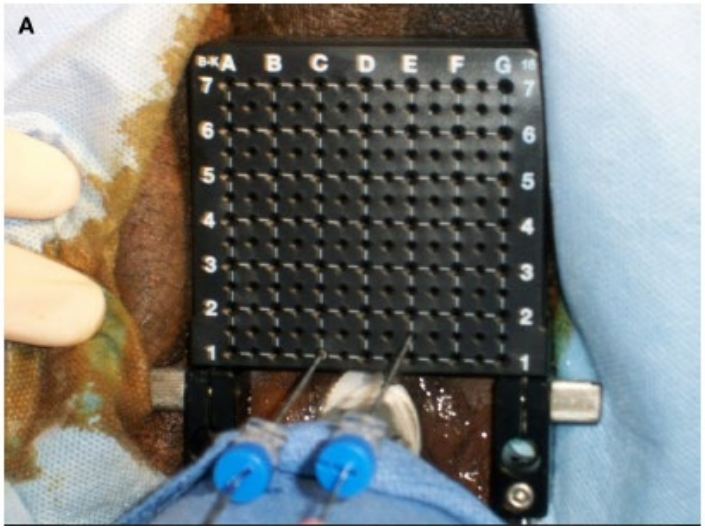
Treatment Techniques

- Isocentric (Linac gantry based) vs. non-isocentric (Cyberknife)
- Coplanar vs. non-coplanar beams
- Static gantry angle IMRT vs. Volumetric arc modulated treatment (VMAT)
- Image guidance: kV imaging using fiducial markers or cone beam CT (CBCT)

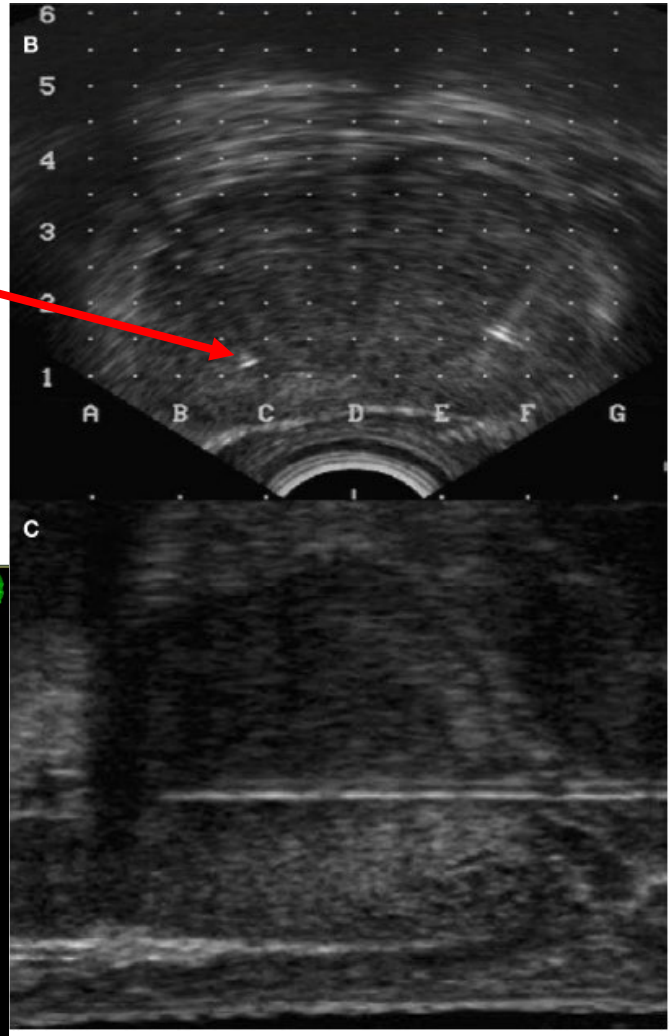
Prostate Targeting / Rectal Spacer Placement

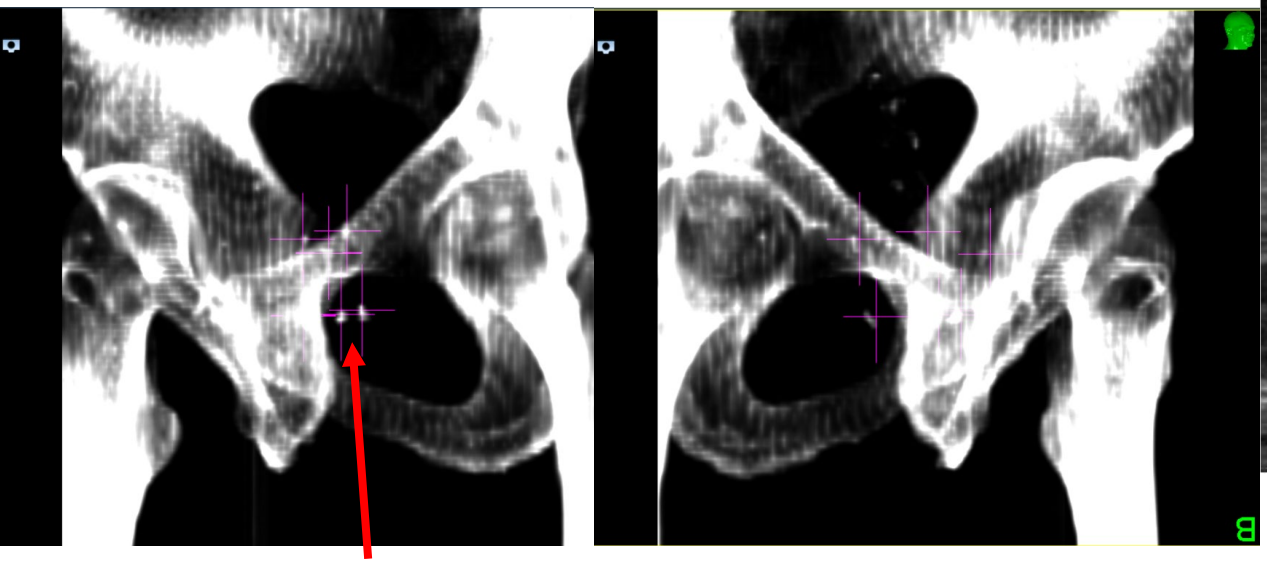
- Six gold prostate fiducial markers and a SpaceOAR were placed under ultrasound guidance
  - At least 3 fiducial markers are needed for tracking – four or more can be placed in case there is displacement or placement outside of prostate
  - The markers have to be in different planes to allow for translational/rotational adjustments
- Patient underwent an mpMRI prostate on the same day as a CT simulation one week after the fiducial/SpaceOAR placement
- Hamstra *et al* Phase III randomized trial IJROBP 2017
  - 222 patients randomized 2:1 to the SpaceOAR vs control and received 79.2 Gy in 44 fractions
  - 3-year grade >= 1 (9.2% vs 2.0%) and grade >= 2 (5.7% vs 0%) rectal toxicity favored the hydrogel spacer
  - QOL was superior in the SpaceOAR group

Fiducial Marker Placement



Fiducial marker

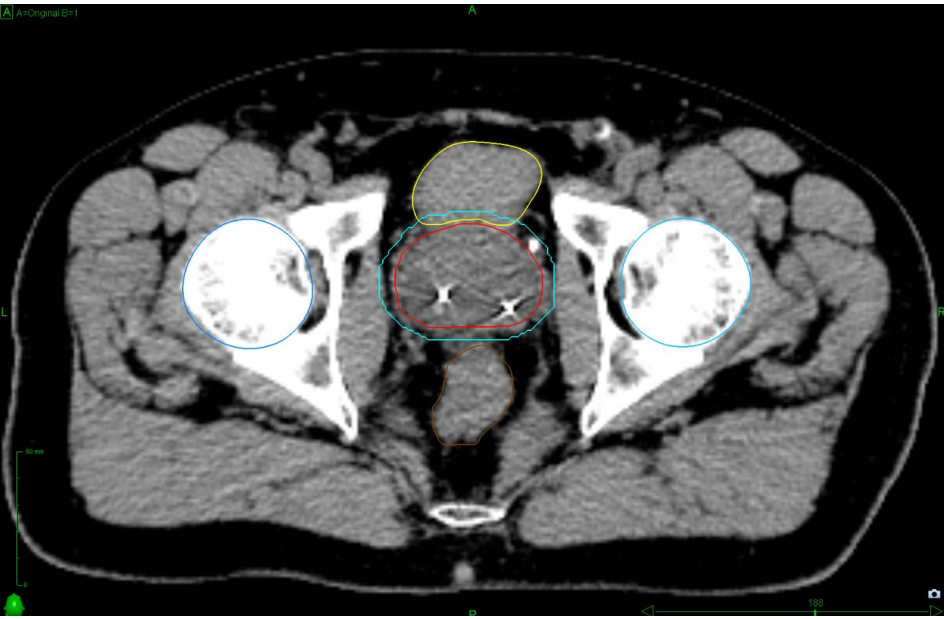


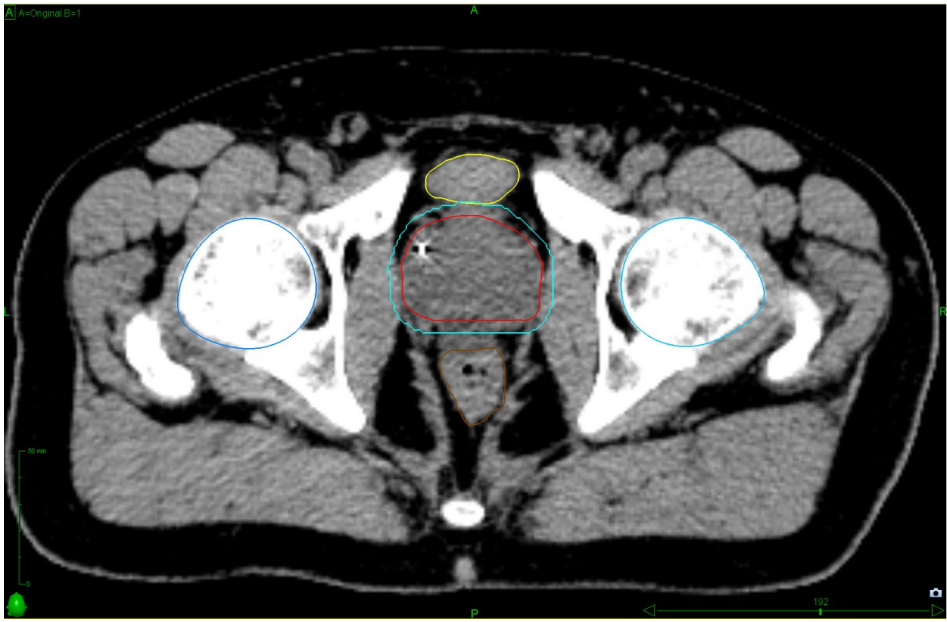


Fiducial marker tracking on Cyberknife (purple crosses over the white fiducial markers)

Lei *et al* Frontiers in Oncology 2011

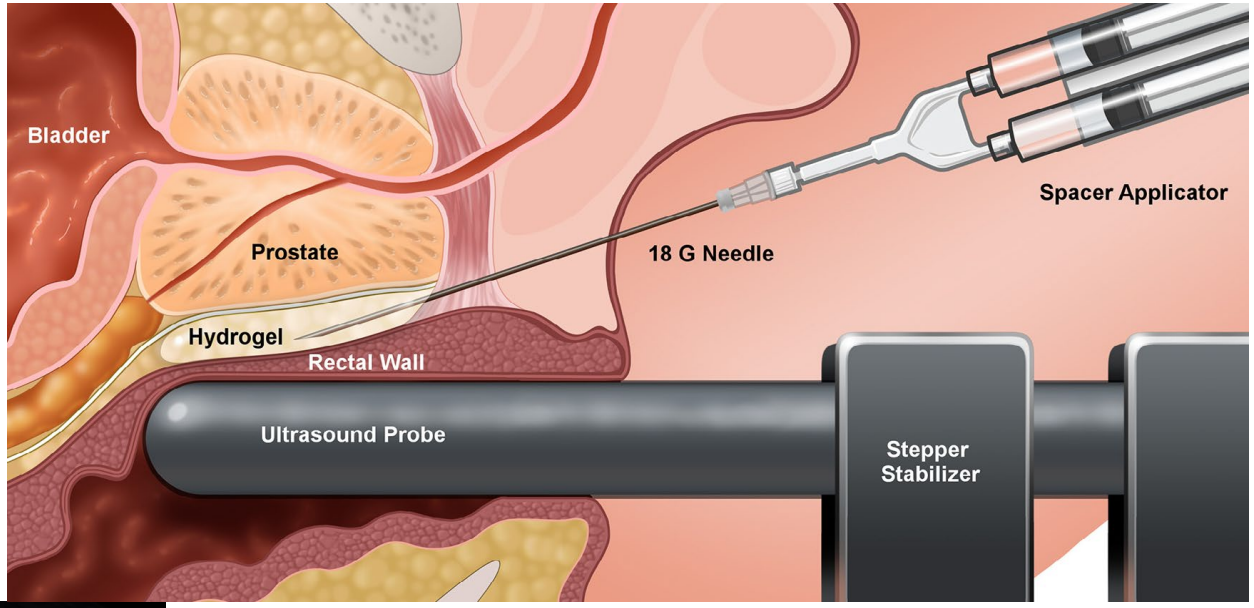
Fiducial Markers: CT Simulation

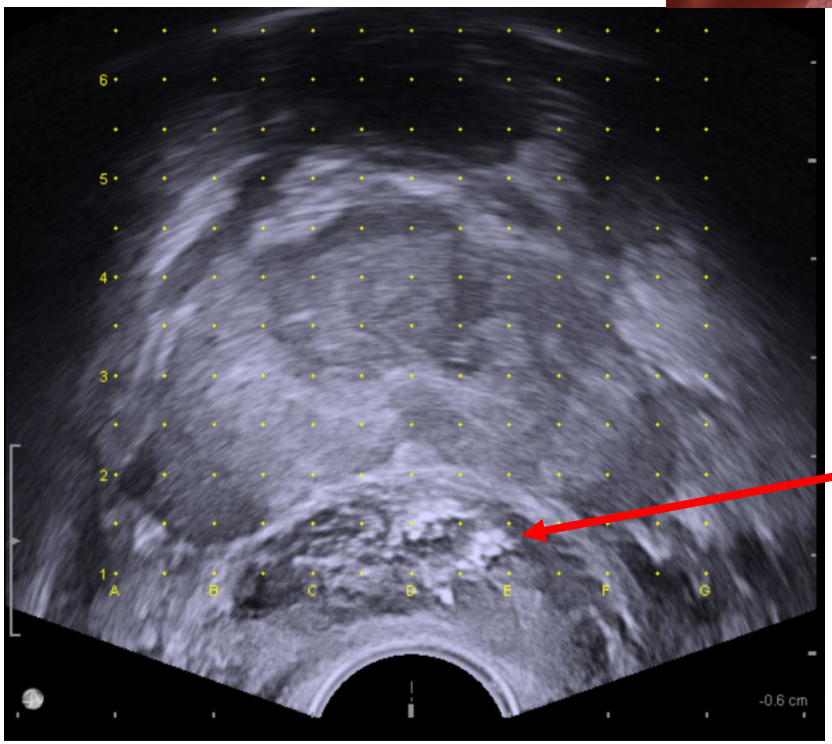


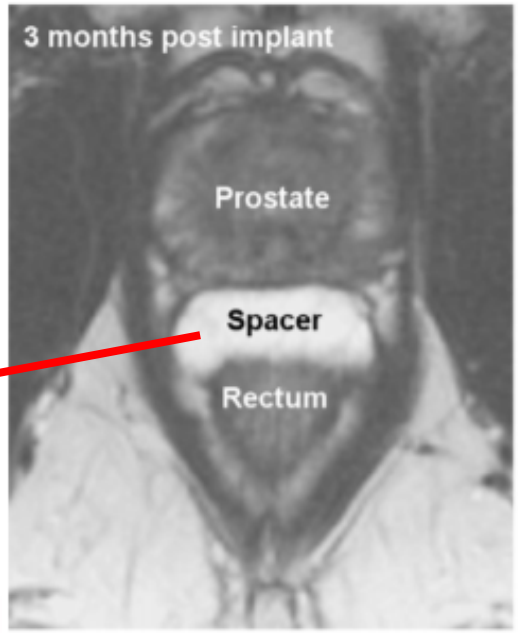


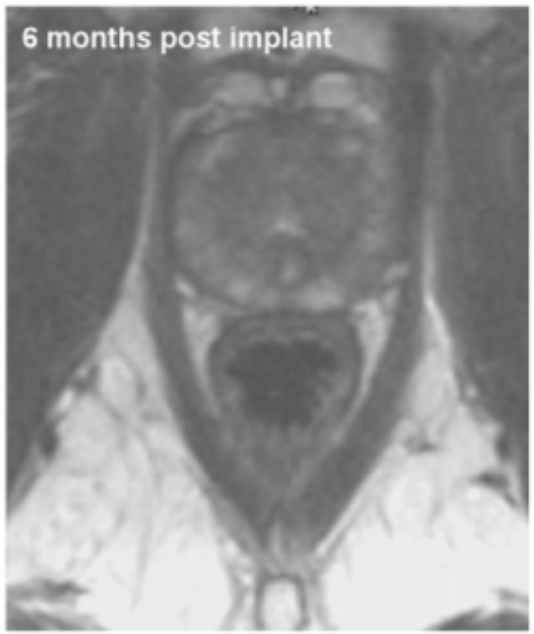
SpaceOAR

Karsh *et al* Urology 2018.







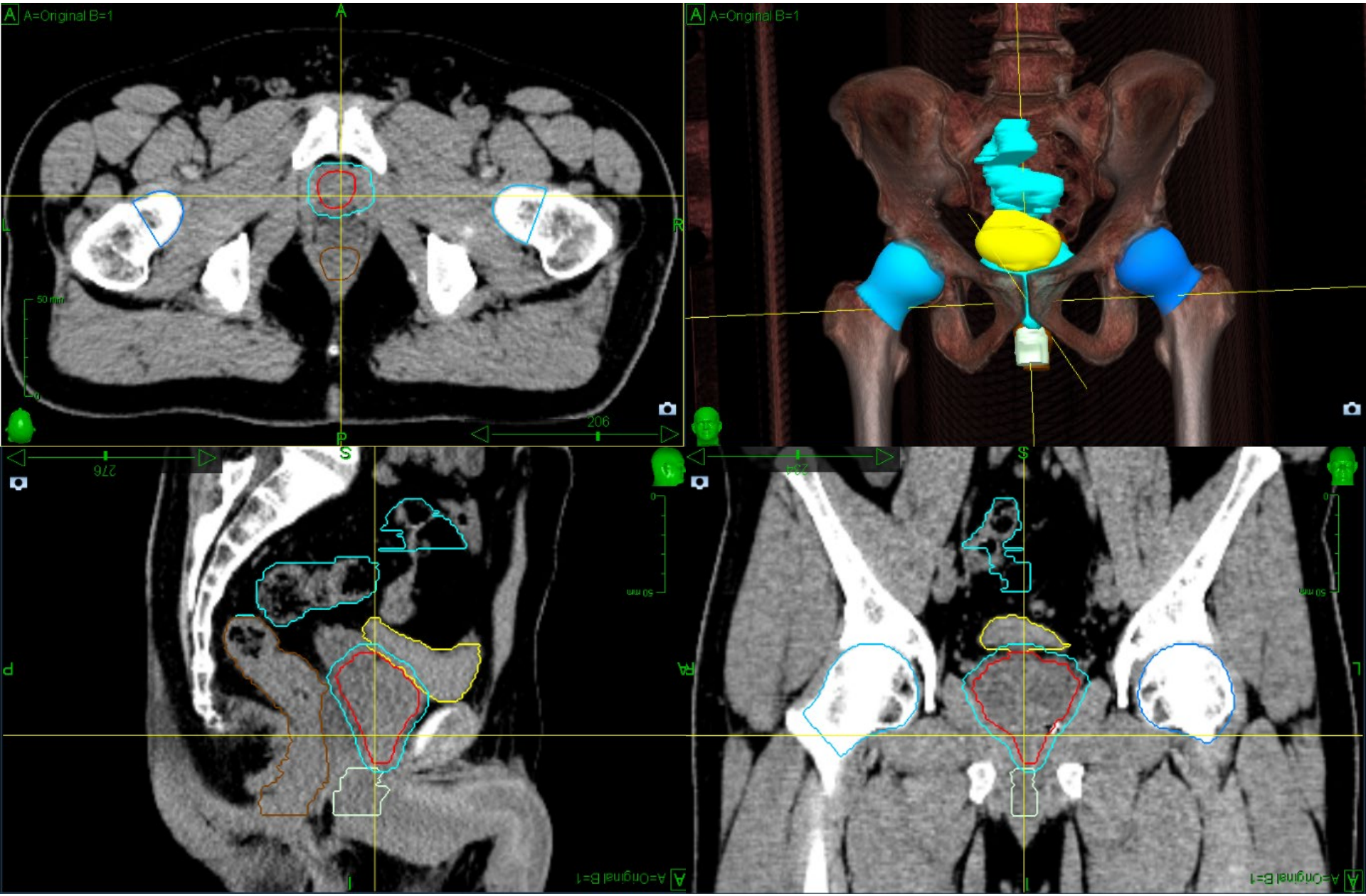


Treatment Planning

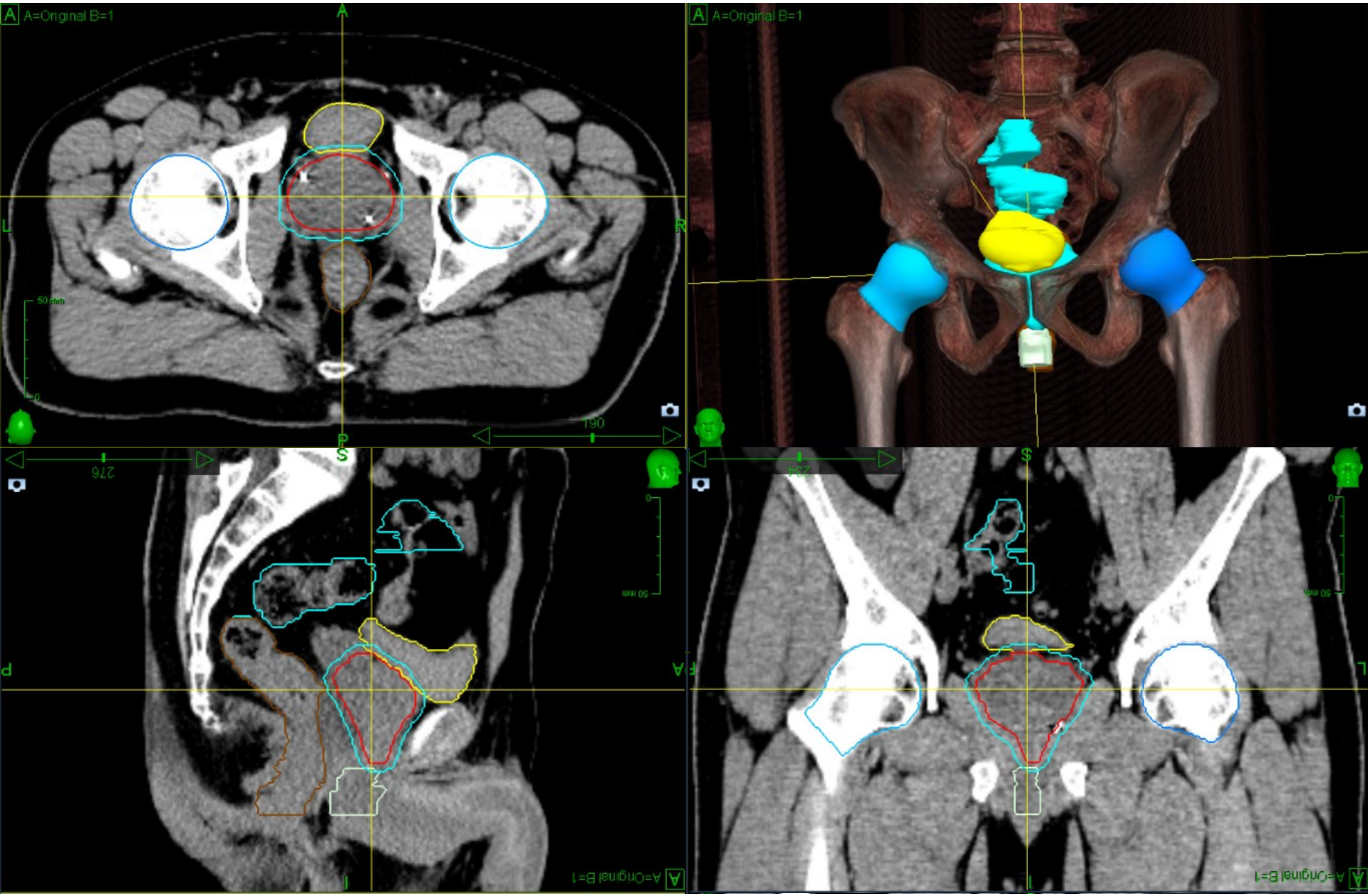
- Patient was CT-simulated supine with arms over chest holding a ring in a vac loc bag with a comfortably full bladder and non-distended rectum
- CTV = prostate on T2-MRI fused with CT sim scan
- PTV = CTV + 5 mm in all directions except for 3 mm posteriorly
- Organs at risk were delineated and used as avoidance structures
- Cyberknife 6X photons were utilized
- kV imaging was used to ensure that the fiducial markers were in the correct position for treatment
- Treatments were administered every other day
- ASCO/ASTRO/AUA does not recommend consecutive daily treatments due to potential increased risk of late urinary and rectal toxicity
- He was treated to 3625 cGy in 5 fractions SBRT on CyberKnife
- A concomitant boost to 4000 cGy is done at some centers based on the PACE-B trial, but we do not do this

Tumor and OAR Delineation

- Prostate T2-weighed MRI mandatory for treatment planning due to superior soft tissue visualization
- Use both the MRI and CT
- Help with contouring: http://www.prostadoodle.com/ and https://econtour.org/training/intact_prostate_module.pdf



red: prostate; green: penile bulb, brown: rectum, yellow: bladder, cyan: small bowel and PTV expansion



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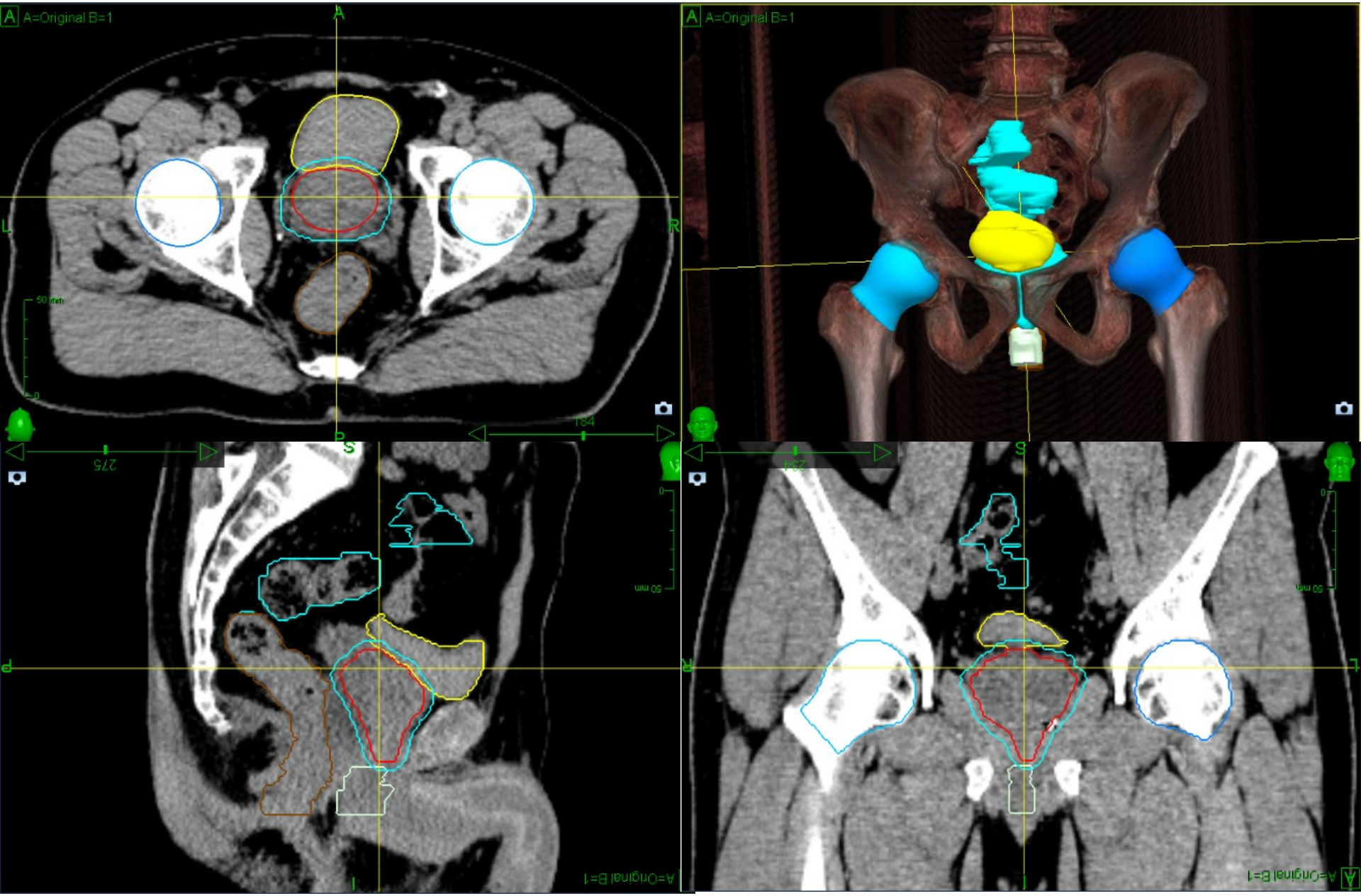

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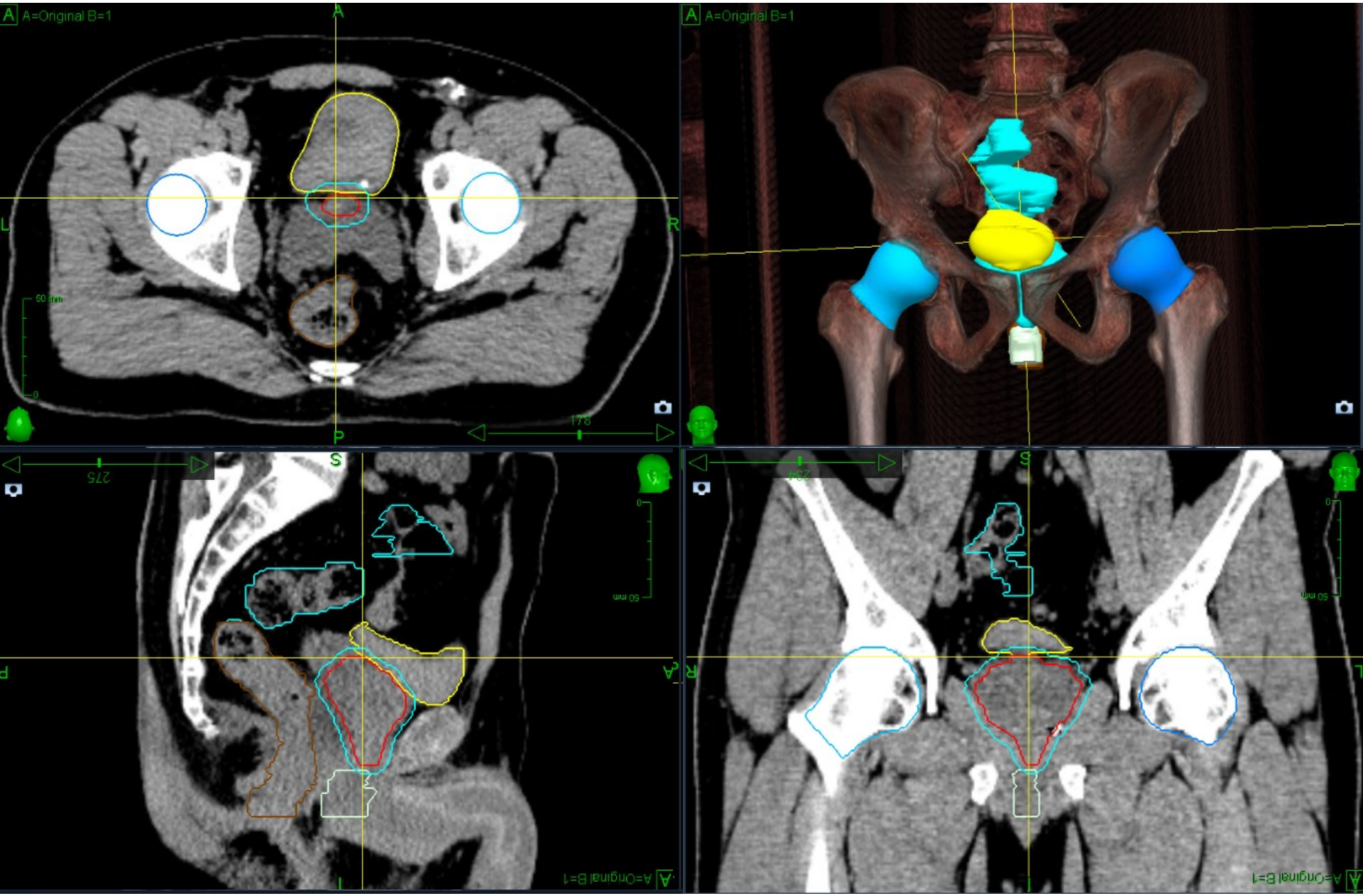
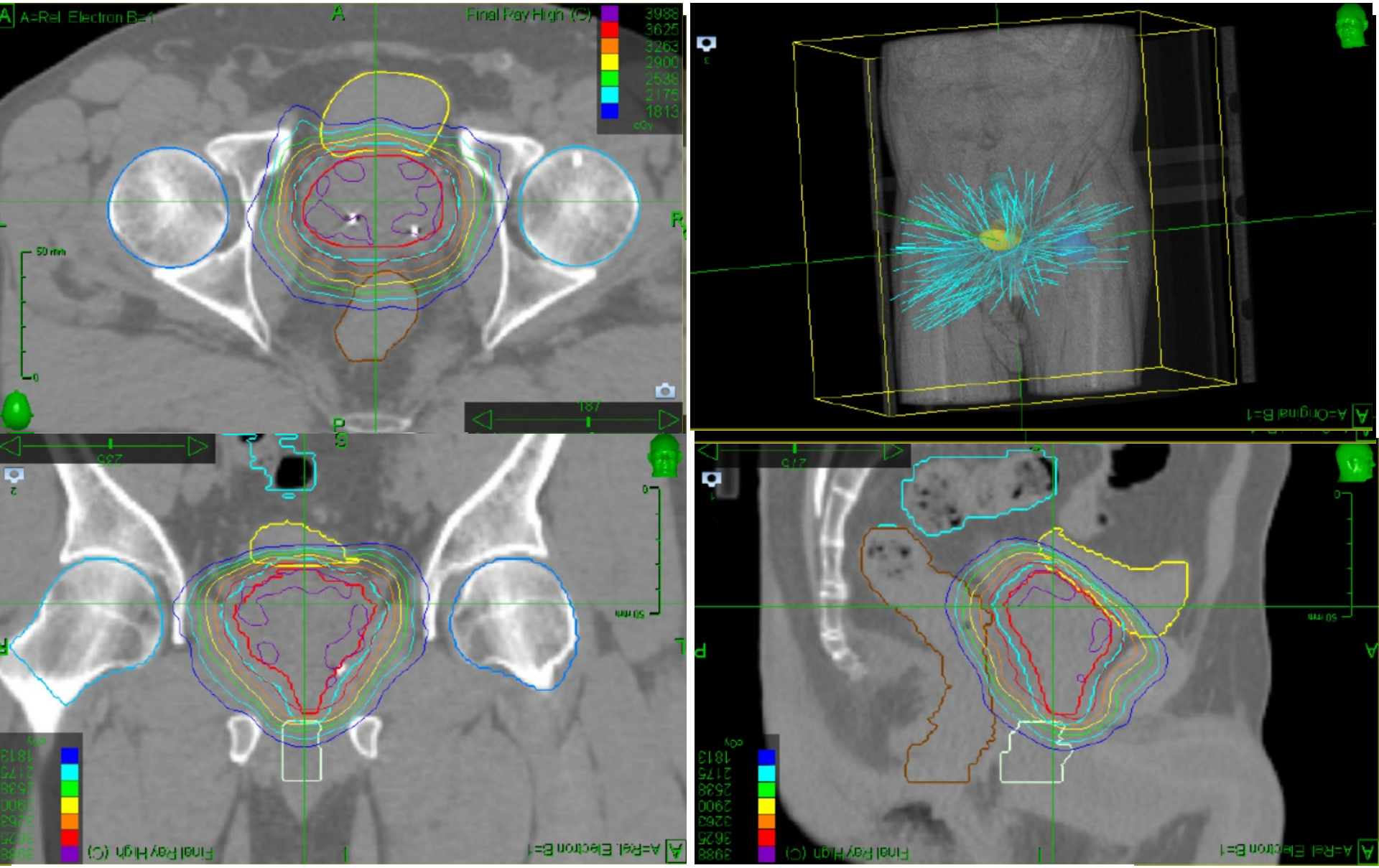


red: prostate; green: penile bulb, brown: rectum, yellow: bladder, cyan: small bowel and PTV expansion



purple: 3988 cGy (110%); red: 3625 cGy (100%); orange: 3263 cGy (90%); yellow: 2900 cGy (80%); green: 2538 cGy (70%); cyan: 2175 cGy (60%); blue 1813 cGy (50%)

Dose Constraints from GU005

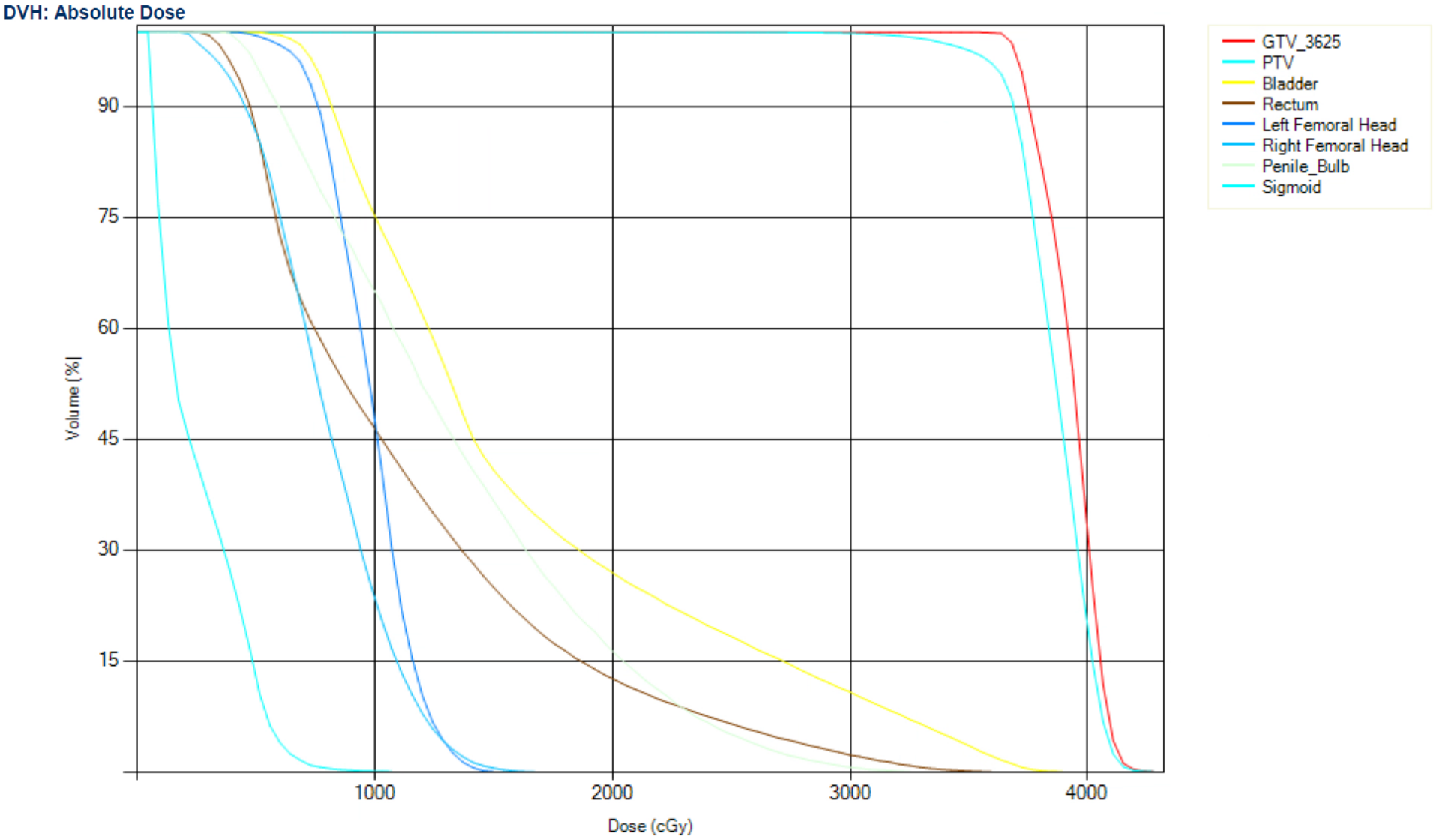
- We followed the NRG GU005 dose constraints:

Name of Structure	Dosimetric parameter*	Per Protocol	Variation Acceptable	Notes
PTV_3625	D0.03cc[Gy]	<= 38.78	<=43.5	**Arm 2**
	D99% [Gy]	>=34.4	>=33.7	
	D98%[Gy]	>=36.25	>=34.4	

Structure	**Dosimetric Parameter**	**Acceptable**
Penile Bulb	D0.03cc[%]	<= 100
	D3cc[%]	<= 55 (19.9Gy)
Femurs	D10cc[%]	<= 43 (15.6Gy)
	D1cc[%]	<= 55 (19.9Gy)
E-PTV-OAR***	D10cc[%]	<= 30 (10.9Gy)
	D1cc[%]	<= 43 (15.6Gy)

Dose Constraints from GU005

Name of	Dosimetric parameter*	Per Protocol	Variation Acceptable	
Rectum	D0.03cc[Gy]	<=38.06	< 40	
	D3cc[Gy]	< =34.4	< 36	
	D10%[Gy]	<= 32.63	< 34	
	D20%[Gy]	<= 29	< 30	
	D50%[Gy]	<=18.13	< 19	
Bladder	D0.03cc[Gy]	<=38.06	< 40	
	D50% [Gy]	<=18.12	< 20	
Spc_Bowel	D0.03cc[Gy]	<=30	<33	
Urethra	D0.03cc[Gy]	<=38.78	43.5	For patients where the maximum point dose to a point that is 0.03 cc exceeds 38.78 Gy, visualization of the urethra is required


DVH: Absolute Dose
GTV_3625
PTV
Bladder
Rectum
Left Femoral Head
Right Femoral Head
Penile_Bulb
Sigmoid
90
75
60
45
30
15
Volume [%]
1000
2000
3000
4000
Dose (cGy)

VOI List

VOI	Volume (cm^3)	Min (cGy)	Mean (cGy)	Max (cGy)	CI	nCI	HI	Coverage %	Beam Inter.
GTV_3625	50.26	3474	3933	4280	1.85	1.85	1.18	99.88	n/a
PTV	89.50	2648	3865	4280	1.09	1.15	1.18	94.93	n/a
Bladder	55.20	517	1637	3877	n/a	n/a	n/a	n/a	Allowed
Rectum	57.99	251	1135	3598	n/a	n/a	n/a	n/a	Allowed
Urethra	3.28	3352	3721	3829	n/a	n/a	n/a	n/a	Allowed
Left Femoral Head	69.47	409	980	1491	n/a	n/a	n/a	n/a	Allowed
Right Femoral Head	71.39	200	796	1651	n/a	n/a	n/a	n/a	Allowed
Penile_Bulb	9.19	378	1338	3225	n/a	n/a	n/a	n/a	Allowed
Skin-15	351.96	51	193	1337	n/a	n/a	n/a	n/a	Allowed
Testicle block	133.55	58	68	76	n/a	n/a	n/a	n/a	Exit Only
Sigmoid	80.43	75	253	1072	n/a	n/a	n/a	n/a	Allowed
Fiducials	0.74	3554	3922	4125	n/a	n/a	n/a	n/a	Allowed
SpaceOAR	13.35	2083	3507	4059	n/a	n/a	n/a	n/a	Allowed
ISO 1813 cGy	353.60	1813	2909	4280	n/a	n/a	n/a	n/a	Allowed
[PTV] Shell 3	54.47	127	757	1423	0.00	0.00	0.00	0.00	Allowed
[PTV] Shell 2	31.42	382	1411	2083	0.00	0.00	0.00	0.00	Allowed
[PTV] Shell 1	14.08	1739	3179	3760	0.00	0.00	0.00	0.00	Allowed
All Target Regions	n/a	2648	3865	4280	1.09	1.15	1.18	94.93	n/a
All Critical Regions	n/a	51	1169	4280	0.00	0.00	0.00	0.00	n/a
Soft Tissue	n/a	32	120	4280	0.00	0.00	0.00	0.00	n/a

Post-treatment Considerations

- Chronic GU, GI and sexual toxicity: counsel the patients and know the timeline of side effects with SBRT
- Routine follow-ups with PSA assessment: per NCCN guidelines
- PSA bounce after SBRT (Jiang *et al* IJROBP 2019)
  - Occurs in a quarter of patients
  - Median magnitude of PSA bounce: 0.52 ng/mL (IQR: 0.3-1.0) after completion of prostate SBRT
  - Median time to bounce: 18 months (IQR 12 – 31)

Conclusion

- SBRT is an excellent treatment modality for localized prostate cancer endorsed by ASTRO, ASCO, AUA, NCCN and COVID19 pandemic guidelines
- Relatively short follow-up time in prospective studies and few high-risk patients included in the trials are limitations of this technique
- While oncologic outcomes appear to be comparable with other EBRT techniques, side effects occur earlier but resolve sooner
- Careful patient selection is needed
- Technological advances: image-guided radiotherapy, SpaceOAR, fiducial markers, MRI-based radiotherapy and robotic SBRT
- Enrollment in ongoing randomized trials such as NRG GU005 and HEAT is strongly encouraged

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